

## ORALLY ADMINISTERED DOSAGE FORMS OF FUSED GABA ANALOG PRODRUGS HAVING REDUCED TOXICITY

This application claims the benefit under 35 U.S.C. § 119(e) from United States Provisional Application Serial No. 60/432,931 filed December 11, 2002, and United States Provisional Application Serial No. 60/433,243 filed December 12, 2002, which are herein incorporated by reference, in their entirety.

### 1. Field of the Invention

The present invention relates generally to prodrugs of fused GABA analogs which are adapted to be administered orally, and dosage forms for administering these prodrugs of fused GABA analogs to reduce their toxicity.

### 2. Background of the Invention

Gamma ("γ")-aminobutyric acid ("GABA") is one of the major inhibitory transmitters in the central nervous system of mammals. GABA is not transported efficiently into the brain from the bloodstream (*i.e.*, GABA does not effectively cross the blood-brain barrier). Consequently, brain cells provide virtually all of the GABA found in the brain (GABA is biosynthesized by decarboxylation of glutamic acid with pyridoxal phosphate).

GABA regulates neuronal excitability through binding to specific membrane proteins (*i.e.*, GABAA receptors), which results in opening of an ion channel. The entry of chloride ion through the ion channel leads to hyperpolarization of the recipient cell, which consequently prevents transmission of nerve impulses to other cells. Low levels of GABA have been observed in individuals suffering from epileptic seizures, motion disorders (*e.g.*, multiple sclerosis, action tremors, tardive dyskinesia), panic, anxiety, depression, alcoholism and manic behavior.

The implication of low GABA levels in a number of common disease states and/or common medical disorders has stimulated intensive interest in preparing GABA analogs, which have superior pharmaceutical properties in comparison to GABA (*e.g.*, the ability to cross the blood brain barrier). Accordingly, a number of GABA analogs, with considerable pharmaceutical activity have been synthesized in the art (See, *e.g.*, Satzinger *et al.*, United States Patent No. 4,024,175; Silverman *et al.*, United States Patent No. 5,563,175; Horwell *et al.*, United States Patent No. 6,020,370; Silverman *et al.*, United States Patent No.

6,028,214; Horwell *et al.*, United States Patent No. 6,103,932; Silverman *et al.*, United States Patent No. 6,117,906; Silverman, International Publication No. WO 92/09560; Silverman *et al.*, International Publication No. WO 93/23383; Horwell *et al.*, International Publication No. WO 97/29101, Horwell *et al.*, International Publication No. WO 97/33858; 5 Horwell *et al.*, International Publication No. WO 97/33859; Bryans *et al.*, International Publication No. WO 98/17627; Guglietta *et al.*, International Publication No. WO 99/08671; Bryans *et al.*, International Publication No. WO 99/21824; Bryans *et al.*, International Publication No. WO 99/31057; Belliotti *et al.*, International Publication No. WO 99/31074; Bryans *et al.*, International Publication No. WO 99/31075; Bryans *et al.*, 10 International Publication No. WO 99/61424; Bryans *et al.*, International Publication No. WO 00/15611; Bryans, International Publication No. WO 00/31020; Bryans *et al.*, International Publication No. WO 00/50027; Bryans *et al.*, International Publication No. WO 02/00209; Blackwell *et al.*, International Publication No. WO 02/085839).

However, many GABA analogs, including those described above exhibit poor oral 15 absorption across the gut wall. One potential solution to the above problem is converting GABA analogs to prodrugs of GABA analogs (Bryans *et al.*, International Publication No. WO 01/90052; U.K. Application GB 2,362,646; European Applications EP 1,201,240 and 1,178,034; Yatvin *et al.*, United States Patent No. 6,024,977; Gallop *et al.*, United States Patent Application Serial No. 10/171,485, filed June 11, 2002; Gallop *et al.*, International 20 Publication No. WO 02/28881; Gallop *et al.*, International Publication No. WO 02/28883; Gallop *et al.*, International Publication No. WO 02/28411; Gallop *et al.*, International Publication No. WO 02/32376; Gallop *et al.*, International Publication No. WO 02/42414). Typically, in a prodrug, a polar functional group (*e.g.*, a carboxylic acid, an amino group, a hydroxyl group, *etc.*) is masked by a promoiety, which is labile under physiological 25 conditions. Accordingly, prodrugs are usually transported through hydrophobic biological barriers such as membranes and typically possess superior physicochemical properties in comparison to the parent drug.

Pharmacologically effective prodrugs are ideally non-toxic and are preferably selectively cleaved at the locus of drug action. Ideally, cleavage of the promoiety occurs 30 rapidly and quantitatively with the formation of non-toxic by-products (*i.e.*, the hydrolyzed promoiety).

Many GABA analog prodrugs exhibit unacceptable toxicity when administered orally in conventional dosage forms. In part this is due to the high doses required for many

GABA analog therapy and in part because most of the therapeutic indications for GABA analogs require long-term chronic administration (*i.e.*, administration for periods of months, years or even for the remaining lifetime of the patient). Additional problems may be caused by the chemical structure of the promoiety, which may hydrolyze to toxic metabolites (*e.g.*, aldehydes or acids).

Accordingly, what is needed is a method for reducing toxicity when administering prodrugs of GABA analogs. Ideally, the above method is particularly effective when the promoiety hydrolyzes to provide toxic metabolites.

### 3. Summary of the Invention

The present invention addresses these and other needs by providing oral dosage forms for prodrugs of fused GABA analogs which exhibit lower toxicity than conventional oral dosage forms of these same prodrugs. The oral dosage form of the present invention has particular utility in administering prodrugs of fused GABA analogs which are metabolized to form an aldehyde. In addition, the dosage forms of the present invention may be used to administer prodrugs of fused GABA analogs which are metabolized to form acids which deplete the body's carnitine reserves. The present invention also provides methods for treating patients using these dosage forms.

In one aspect, the current invention comprises an oral sustained release dosage form for administering a prodrug of a fused GABA analog. In another aspect, the invention comprises a method of reducing toxicity of orally administered fused GABA analogs. The above method includes making a prodrug of a fused GABA analog, the prodrug, having a cleavable promoiety covalently bound to the therapeutic fused GABA analog covalently bound to a cleavable promoiety. The fused GABA analog prodrug is placed in a sustained release oral dosage form and the dosage form is introduced into an intestinal lumen of a patient by having the patient swallow the dosage form. The method further includes releasing the prodrug gradually from the swallowed dosage form into the intestinal lumen of the patient over a period of hours and allowing the fused GABA analog to be cleaved from the promoiety after swallowing to provide a therapeutic concentration of the fused GABA analog in the blood plasma of the patient. When following this method, the toxicity of the prodrug of the fused GABA analog is less than a toxicity of an equivalent dose of the prodrug administered from an immediate release oral dosage form. In one preferred embodiment, the prodrug is metabolized to form an aldehyde (*e.g.*, formaldehyde). In

another embodiment, the prodrug is metabolized to form an acid which depletes the body's carnitine reserves, (e.g., pivalic acid).

Preferably, the prodrug is released from the dosage form over a period of at least about 6 hours, more preferably, over a period of at least about 8 hours, and most preferably, over a period of at least about 12 hours. Further, the dosage form preferably releases from 0 to 20% of the prodrug in 0 to 2 hours, from 20 to 50% of the prodrug in 2 to 12 hours, from 50 to 85% of the prodrug in 3 to 20 hours and greater than 75% of the prodrug in 5 to 18 hours.

In a preferred embodiment, the current invention provides an oral dosage form of a prodrug of a fused GABA analog, wherein the dosage form, upon swallowing, provides a curve of concentration of the fused GABA analog in the plasma over time, the curve having an area under the curve (AUC) which is proportional to the dose of fused GABA analog administered, and preferably, also has a maximum concentration  $C_{max}$  that is proportional to the dose of fused GABA analog administered. In one embodiment, the  $C_{max}$  is less than 75%, and is preferably less than 60%, of the  $C_{max}$  obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form. Preferably, the AUC is at least 50% of the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form, more preferably, at least 75% of the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form and most preferably, substantially the same as, the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

The oral sustained release dosage forms of the present invention can take any form as long as the release characteristics and pharmacokinetic profiles above are satisfied. For example, the dosage form can be in the form of an osmotic dosage form, a prodrug-releasing polymer, prodrug-releasing tiny timed-release pills, prodrug-releasing lipids, prodrug-releasing waxes and/or prodrug releasing beads.

The dosage forms and administration methods of the present invention may be useful for treating or preventing epilepsy, depression, anxiety, psychosis, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, panic, pain (especially, neuropathic pain and muscular and skeletal pain), inflammatory disease (i.e., arthritis), insomnia, gastrointestinal disorders or ethanol withdrawal syndrome.

## Specific Embodiments of the Invention

### Definitions

5       “Active transport or active transport process” refers to the movement of molecules across cellular membranes that:

        a)       is directly or indirectly dependent on an energy mediated process (*i.e.*, driven by ATP hydrolysis, ion gradient, *etc.*);

        or

10       b)       occurs by facilitated diffusion mediated by interaction with specific transporter proteins.

        “Alkyl” by itself or as part of another substituent refers to a saturated or unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne.

15       Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 20       2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

        The term “alkyl” is specifically intended to include groups having any degree or level of saturation, *i.e.*, groups having exclusively single carbon-carbon bonds, groups 25       having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific level of saturation is intended, the expressions “alkanyl,” “alkenyl,” and “alkynyl” are used. Preferably, an alkyl group comprises from 1 to 20 carbon atoms, more preferably, from 1 to 10 carbon atoms, even more preferably, from 1 to 30       6 carbon atoms.

        “Alkanyl” by itself or as part of another substituent refers to a saturated branched, straight-chain or cyclic alkyl radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited

to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, *etc.*; butanyls such as butan-1-yl, butan-2-yl (*sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (*t*-butyl), cyclobutan-1-yl, *etc.*; and the like.

5           “Alkenyl” by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as  
10 prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, *etc.*; and the like.

15           “Alkynyl” by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, *etc.*; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl,  
20 but-3-yn-1-yl, *etc.*; and the like.

          “Acyl” by itself or as part of another substituent refers to a radical  $-C(O)R^{30}$ , where  $R^{30}$  is hydrogen, alkyl, cycloalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl as defined herein. Representative examples include, but are not limited to formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl  
25 and the like.

          “Alkylamino” by itself or as part of another substituent refers to a radical  $-NHR^{31}$  where  $R^{31}$  represents an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methylamino, ethylamino, 1-methylethylamino, cyclohexyl amino and the like.

30           “Alkoxy” by itself or as part of another substituent refers to a radical  $-OR^{32}$  where  $R^{32}$  represents an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, cyclohexyloxy and the like.

“Alkoxy carbonyl” by itself or as part of another substituent refers to a radical – C(O)OR<sup>32</sup> where R<sup>32</sup> represents an alkyl or cycloalkyl group as defined herein.

Representative examples include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, cyclohexyloxycarbonyl and the like.

5        “Aryl” by itself or as part of another substituent refers to a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, 10        hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. Preferably, an aryl group comprises from 6 to 20 carbon atoms, more preferably from 6 to 12 carbon atoms.

15        “Arylalkyl” by itself or as part of another substituent refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or *sp*<sup>3</sup> carbon atom, is replaced with an aryl group. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and 20        the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylalkenyl and/or arylalkynyl is used. Preferably, an arylalkyl group is (C<sub>6</sub>-C<sub>30</sub>) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C<sub>1</sub>-C<sub>10</sub>) and the aryl moiety is (C<sub>6</sub>-C<sub>20</sub>), more preferably, an arylalkyl group is (C<sub>6</sub>-C<sub>20</sub>) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C<sub>1</sub>-C<sub>8</sub>) and the aryl moiety is 25        (C<sub>6</sub>-C<sub>12</sub>).

“AUC” is the area under the plasma drug concentration-versus-time curve extrapolated from zero time to infinity.

“Carbamoyl” by itself or as part of another substituent refers to the radical -C(O)N(R<sup>33</sup>)R<sup>34</sup> where R<sup>33</sup> and R<sup>34</sup> are independently hydrogen, alkyl, substituted alkyl, 30        aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroarylalkyl, substituted heteroarylalkyl, heteroaryl or substituted heteroaryl, as defined herein.

“Carcinogenic potency (TD<sub>50</sub>)” (see Peto *et al.*, *Environmental Health Perspectives* 1984, 58, 1-8) is defined for a particular compound in a given animal species as that chronic

dose-rate in mg/kg body wt/day which would induce tumors in half the test animals at the end of a standard lifespan for the species. Since the tumor(s) of interest often does occur in control animals, TD<sub>50</sub> is more precisely defined as: that dose-rate in mg/kg body wt/day which, if administered chronically for the standard lifespan of the species, will halve the probability of remaining tumorless throughout that period. A TD<sub>50</sub> can be computed for any particular type of neoplasm, for any particular tissue, or for any combination of these.

"C<sub>max</sub>" is the highest drug concentration observed in plasma following an extravascular dose of drug.

"Compounds used in the invention" refers to compounds encompassed by the generic formulae disclosed herein and includes any specific compounds within those formulae whose structure is disclosed herein. The compounds of the invention may be identified either by their chemical structure and/or chemical name. When the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds of the invention may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers or diastereomers. Accordingly, when stereochemistry at chiral centers is not specified, the chemical structures depicted herein encompass all possible configurations at those chiral centers including the stereoisomerically pure form (*e.g.*, geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the skilled artisan. The compounds of the invention may also exist in several tautomeric forms including the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. The compounds of the invention also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds of the invention include, but are not limited to, <sup>2</sup>H, <sup>3</sup>H, <sup>13</sup>C, <sup>14</sup>C, <sup>15</sup>N, <sup>18</sup>O and <sup>17</sup>O. Compounds of the invention may exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In general, the hydrated, solvated and N-oxide forms are within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present



invention and are intended to be within the scope of the present invention. Further, it should be understood, when partial structures of the compounds of the invention are illustrated, that brackets indicate the point of attachment of the partial structure to the rest of the molecule.

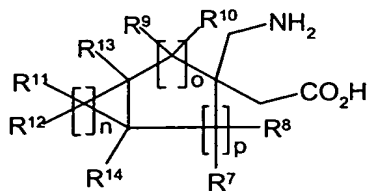
5           “Cycloalkyl” by itself or as part of another substituent refers to a saturated or unsaturated cyclic alkyl radical. Where a specific level of saturation is intended, the nomenclature “cycloalkanyl” or “cycloalkenyl” is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and the like. Preferably, the cycloalkyl group is (C<sub>3</sub>–C<sub>10</sub>) cycloalkyl, more  
10           preferably (C<sub>3</sub>–C<sub>7</sub>) cycloalkyl.

          “Cycloheteroalkyl” by itself or as part of another substituent refers to a saturated or unsaturated cyclic alkyl radical in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S, Si, *etc.*  
15           Where a specific level of saturation is intended, the nomenclature “cycloheteroalkanyl” or “cycloheteroalkenyl” is used. Typical cycloheteroalkyl groups include, but are not limited to, groups derived from epoxides, azirines, thiiranes, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine and the like.

          “Derived from a fused GABA analog” refers to a moiety that is structurally related  
20           to a fused GABA analog. The structure of the moiety is identical to the compound except at 1 or 2 positions. At these positions, a hydrogen atom attached to the amino group, and (optionally) the hydroxyl moiety of the carboxylic acid group has been replaced with a covalent bond that serves as a point of attachment to another moiety.

          “Dialkylamino” by itself or as part of another substituent refers a radical –NR<sup>35</sup>R<sup>36</sup>  
25           where R<sup>35</sup> and R<sup>36</sup> are independently an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, dimethylamino, methylethylamino, di-(1-methylethyl)amino, (cyclohexyl)(methyl)amino, (cyclohexyl)(ethyl)amino, (cyclohexyl)(propyl)amino and the like.

          “Fused GABA analog” refers to a compound, unless specified otherwise, as having  
30           the following structure:



wherein:

5           n is 1, 2, 3, 4, 5 or 6

          o is 0, 1, 2 or 3;

          p is 0, 1 or 2; and

10

each of  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted

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heteroarylalkyl.  
“Heteroalkyl, Heteroalkanyl, Heteroalkenyl and Heteroalkynyl” by themselves or as part of another substituent refer to alkyl, alkanyl, alkenyl and alkynyl groups, respectively, in which one or more of the carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatomic groups. Typical  
 20 heteroatomic groups which can be included in these groups include, but are not limited to, -O-, -S-, -O-O-, -S-S-, -O-S-, -NR<sup>37</sup>R<sup>38</sup>-, =N-N=, -N=N-, -N=N-NR<sup>39</sup>R<sup>40</sup>-, -PR<sup>41</sup>-, -P(O)<sub>2</sub>-, -POR<sup>42</sup>-, -O-P(O)<sub>2</sub>-, -SO-, -SO<sub>2</sub>-, -SnR<sup>43</sup>R<sup>44</sup>- and the like, where R<sup>37</sup>, R<sup>38</sup>, R<sup>39</sup>, R<sup>40</sup>, R<sup>41</sup>, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl,  
 25 substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl.

“Heteroaryl” by itself or as part of another substituent refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Typical heteroaryl groups include, but are not limited  
 30 to, groups derived from acridine, arsindeole, carbazole,  $\beta$ -carboline, chromane, chromene,

cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. Preferably, the heteroaryl group is from 5-20 membered heteroaryl, more preferably from 5-10 membered heteroaryl. Preferred heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

“Heteroarylalkyl” by itself or as part of another substituent refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or  $sp^3$  carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkenyl, heteroarylalkenyl and/or heteroarylalkynyl is used. In preferred embodiments, the heteroarylalkyl group is a 6-30 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is 1-10 membered and the heteroaryl moiety is a 5-20-membered heteroaryl, more preferably, 6-20 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is 1-8 membered and the heteroaryl moiety is a 5-12-membered heteroaryl.

“Oxycarbonyl” by itself or as part of another substituent refers to a radical  $-C(O)-OR^{45}$  where  $R^{45}$  represents an alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl group as defined herein. Representative examples include, but are not limited to, methoxycarbonyl, piperidineoxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and the like.

“Parent Aromatic Ring System” refers to an unsaturated cyclic or polycyclic ring system having a conjugated  $\pi$  electron system. Specifically included within the definition of “parent aromatic ring system” are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, *etc.* Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene,

ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like.

5       “Parent Heteroaromatic Ring System” refers to a parent aromatic ring system in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atoms include, but are not limited to, N, P, O, S, Si, *etc.* Specifically included within the definition of “parent heteroaromatic ring systems” are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, 10 such as, for example, arsindole, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, *etc.* Typical parent heteroaromatic ring systems include, but are not limited to, arsindole, carbazole,  $\beta$ -carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, 15 perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like.

20       “Passive diffusion” refers to uptake of an agent that is not mediated by a specific transporter protein. An agent that is substantially incapable of passive diffusion has a permeability across a standard cell monolayer (*e.g.*, Caco-2) *in vitro* of less than  $5 \times 10^{-6}$  cm/sec, and usually less than  $1 \times 10^{-6}$  cm/sec (in the absence of an efflux mechanism).

25       “Pharmaceutical composition used in the invention” refers to at least one fused GABA analog prodrug used in the invention and a pharmaceutically acceptable vehicle, with which the prodrug is administered to a patient. When administered to a patient, the prodrugs are administered in isolated form, which means separated from a synthetic organic reaction mixture.

30       “Pharmaceutically acceptable salt” refers to a salt of a compound of the invention, which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid,

fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, 5 camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an 10 aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like.

“Pharmaceutically acceptable vehicle” refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

“Patient” includes humans. The terms “human” and “patient” are used 15 interchangeably herein.

“Preventing” or “prevention” refers to a reduction in risk of acquiring a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a patient that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease).

“Prodrug” refers to a derivative of a drug molecule that requires a transformation 20 within the body to release the active drug. Prodrugs are frequently, although not necessarily, pharmacologically inactive until converted to the parent drug. A hydroxyl containing drug may be converted to, for example, to a sulfonate, ester or carbonate prodrug, which may be hydrolyzed *in vivo* to provide the hydroxyl compound. An amino 25 containing drug may be converted, for example, to a carbamate, amide, enamine, imine, N-phosphonyl, N-phosphoryl or N-sulfenyl prodrug, which may be hydrolyzed *in vivo* to provide the amino compound. A carboxylic acid drug may be converted to an ester (including silyl esters and thioesters), amide or hydrazide prodrug, which be hydrolyzed *in vivo* to provide the carboxylic acid compound. Prodrugs for drugs which functional groups 30 different than those listed above are well known to the skilled artisan.

“Promoiety” refers to a form of protecting group that when used to mask a functional group within a drug molecule converts the drug into a prodrug. Typically, the

promoiety will be attached to the drug *via* bond(s) that are cleaved by enzymatic or non-enzymatic means *in vivo*.

“Protecting group” refers to a grouping of atoms that when attached to a reactive functional group in a molecule masks, reduces or prevents reactivity of the functional group.

5 Examples of protecting groups can be found in Green *et al.*, “Protective Groups in Organic Chemistry”, (Wiley, 2<sup>nd</sup> ed. 1991) and Harrison *et al.*, “Compendium of Synthetic Organic Methods”, Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (“CBZ”), *tert*-butoxycarbonyl (“Boc”), trimethylsilyl (“TMS”),  
10 2-trimethylsilyl-ethanesulfonyl (“SES”), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (“Fmoc”), nitro-veratryloxycarbonyl (“NVOC”) and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl  
15 ethers.

“Substituted” refers to a group in which one or more hydrogen atoms are independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, -M, -R<sup>60</sup>, -O<sup>-</sup>, =O, -OR<sup>60</sup>, -SR<sup>60</sup>, -S<sup>-</sup>, =S, -NR<sup>60</sup>R<sup>61</sup>, =NR<sup>60</sup>, -CF<sub>3</sub>, -CN, -OCN, -SCN, -NO, -NO<sub>2</sub>, =N<sub>2</sub>, -N<sub>3</sub>, -S(O)<sub>2</sub>O<sup>-</sup>, -S(O)<sub>2</sub>OH, -S(O)<sub>2</sub>R<sup>60</sup>, -OS(O<sub>2</sub>)O<sup>-</sup>,  
20 -OS(O)<sub>2</sub>R<sup>60</sup>, -P(O)(O<sup>-</sup>)<sub>2</sub>, -P(O)(OR<sup>60</sup>)(O<sup>-</sup>), -OP(O)(OR<sup>60</sup>)(OR<sup>61</sup>), -C(O)R<sup>60</sup>, -C(S)R<sup>60</sup>, -C(O)OR<sup>60</sup>, -C(O)NR<sup>60</sup>R<sup>61</sup>, -C(O)O<sup>-</sup>, -C(S)OR<sup>60</sup>, -NR<sup>62</sup>C(O)NR<sup>60</sup>R<sup>61</sup>, -NR<sup>62</sup>C(S)NR<sup>60</sup>R<sup>61</sup>, -NR<sup>62</sup>C(NR<sup>63</sup>)NR<sup>60</sup>R<sup>61</sup> and -C(NR<sup>62</sup>)NR<sup>60</sup>R<sup>61</sup> where M is independently a halogen; R<sup>60</sup>, R<sup>61</sup>, R<sup>62</sup> and R<sup>63</sup> are independently hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl,  
25 substituted aryl, heteroaryl or substituted heteroaryl, or optionally R<sup>60</sup> and R<sup>61</sup> together with the nitrogen atom to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring; and R<sup>64</sup> and R<sup>65</sup> are independently hydrogen, alkyl, substituted alkyl, aryl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, aryl, substituted aryl, heteroaryl or substituted heteroaryl, or optionally R<sup>64</sup> and R<sup>65</sup> together with  
30 the nitrogen atom to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring. Preferably, substituents include -M, -R<sup>60</sup>, =O, -OR<sup>60</sup>, -SR<sup>60</sup>, -S<sup>-</sup>, =S, -NR<sup>60</sup>R<sup>61</sup>, =NR<sup>60</sup>, -CF<sub>3</sub>, -CN, -OCN, -SCN, -NO, -NO<sub>2</sub>, =N<sub>2</sub>, -N<sub>3</sub>, -S(O)<sub>2</sub>R<sup>60</sup>, -OS(O<sub>2</sub>)O<sup>-</sup>, -OS(O)<sub>2</sub>R<sup>60</sup>, -P(O)(O<sup>-</sup>)<sub>2</sub>, -P(O)(OR<sup>60</sup>)(O<sup>-</sup>), -OP(O)(OR<sup>60</sup>)(OR<sup>61</sup>), -C(O)R<sup>60</sup>, -C(S)R<sup>60</sup>,

-C(O)OR<sup>60</sup>, -C(O)NR<sup>60</sup>R<sup>61</sup>, -C(O)O<sup>-</sup>, -NR<sup>62</sup>C(O)NR<sup>60</sup>R<sup>61</sup>, more preferably, -M, -R<sup>60</sup>, =O, -OR<sup>60</sup>, -SR<sup>60</sup>, -NR<sup>60</sup>R<sup>61</sup>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -S(O)<sub>2</sub>R<sup>60</sup>, -P(O)(OR<sup>60</sup>)(O<sup>-</sup>), -OP(O)(OR<sup>60</sup>)(OR<sup>61</sup>), -C(O)R<sup>60</sup>, -C(O)OR<sup>60</sup>, -C(O)NR<sup>60</sup>R<sup>61</sup>, -C(O)O<sup>-</sup>, most preferably, -M, -R<sup>60</sup>, =O, -OR<sup>60</sup>, -SR<sup>60</sup>, -NR<sup>60</sup>R<sup>61</sup>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -S(O)<sub>2</sub>R<sup>60</sup>, -OP(O)(OR<sup>60</sup>)(OR<sup>61</sup>),  
 5 -C(O)R<sup>60</sup>, -C(O)OR<sup>60</sup>, -C(O)O<sup>-</sup>, where R<sup>60</sup>, R<sup>61</sup> and R<sup>62</sup> are as defined above.

“Therapeutically effective amount” means the amount of a compound that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, *etc.*, of the patient to be treated.

10 “Transporter protein” refers to a protein that has a direct or indirect role in transporting a molecule into and/or through a cell. For example, a transporter protein may be, but is not limited to, solute carrier transporters, co-transporters, counter transporters, uniporters, symporters, antiporters, pumps, equilibrative transporters, concentrative transporters and other proteins, which mediate active transport, energy-dependent transport,  
 15 facilitated diffusion, exchange mechanisms and specific absorption mechanisms. Transporter proteins, may also be, but are not limited to, membrane-bound proteins that recognize a substrate and effect its entry into or exit from a cell by a carrier-mediated transporter or by receptor-mediated transport. A transporter protein, may also be, but is not limited to, an intracellularly expressed protein that participates in trafficking of substrates  
 20 through or out of a cell. Transporter proteins, may also be, but are not limited to, proteins or glycoproteins exposed on the surface of a cell that do not directly transport a substrate but bind to the substrate holding it in proximity to a receptor or transporter protein that effects entry of the substrate into or through the cell. Examples of carrier proteins include: the intestinal and liver bile acid transporters, dipeptide transporters, oligopeptide  
 25 transporters, simple sugar transporters (*e.g.*, SGLT1), phosphate transporters, monocarboxylic acid transporters, P-glycoprotein transporters, organic anion transporters (OAT), and organic cation transporters. Examples of receptor-mediated transport proteins include: viral receptors, immunoglobulin receptors, bacterial toxin receptors, plant lectin receptors, bacterial adhesion receptors, vitamin transporters and cytokine growth factor  
 30 receptors.

“Toxic” and “toxicity” refers to a medically measurable undesirable effect in a patient to which a particular drug has been orally administered. In the case of a prodrug with an aldehyde-producing promoiety, the terms “toxic” and “toxicity” refer to effects such

as carcinogenicity, irritation, mucosal damage, gastritis, hyperkeratosis, elevation of liver enzymes (*e.g.*, transaminases) and fertility impairment. In the case of a prodrug that releases fused GABA analogs upon cleavage, the terms “toxic” and “toxicity” mean an undesirable side-effects, such as somnolence, dizziness, ataxia, choreoathetosis, nystagmus or dyspepsia, caused by an undesirably high concentration of the parent compound in the systemic circulation of the patient.

“Treating” or “treatment” of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (*i.e.*, arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treating” or “treatment” refers to ameliorating at least one physical parameter, which may not be discernible by the patient. In yet another embodiment, “treating” or “treatment” refers to inhibiting the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treating” or “treatment” refers to delaying the onset of the disease or disorder.

Reference will now be made in detail to preferred embodiments of the invention. While the invention will be described in conjunction with the preferred embodiments, it will be understood that it is not intended to limit the invention to those preferred embodiments. To the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims.

#### **Sustained Release Oral Dosage Forms of the Invention**

The present invention can be practiced with a number of different dosage forms, which may be adapted to provide sustained release of a prodrug upon oral administration.

In one embodiment of the invention, the dosage form comprises beads that on dissolution or diffusion release the prodrug over an extended period of hours, preferably, over a period of at least 6 hours, more preferably, over a period of at least 8 hours and most preferably, over a period of at least 12 hours. The prodrug-releasing beads may have a central composition or core comprising a prodrug and pharmaceutically acceptable vehicles, including an optional lubricant, antioxidant and buffer. The beads may be medical preparations with a diameter of about 1 to about 2 mm. Individual beads may comprise doses of the prodrug, for example, doses of up to about 40 mg of prodrug. The beads, in one embodiment, are formed of non-cross-linked materials to enhance their discharge from



the gastrointestinal tract. The beads may be coated with a release rate-controlling polymer that gives a timed release profile.

5 The time release beads may be manufactured into a tablet for therapeutically effective prodrug administration. The beads can be made into matrix tablets by the direct compression of a plurality of beads coated with, for example, an acrylic resin and blended with excipients such as hydroxypropylmethyl cellulose. The manufacture of beads has been disclosed in the art (Lu, *Int. J. Pharm.*, **1994**, 112, 117-124; Pharmaceutical Sciences by Remington, 14<sup>th</sup> ed, pp1626-1628 (1970); Fincher, *J. Pharm. Sci.* **1968**, 57, 1825-1835; Benedikt, United States Patent No. 4,083,949) as has the manufacture of tablets  
10 (Pharmaceutical Sciences, by Remington, 17<sup>th</sup> Ed, Ch. 90, pp1603-1625 (1985).

In another embodiment, an oral sustained release pump may be used (Langer, *supra*; Sefton, **1987**, *CRC Crit Ref Biomed. Eng.* 14:201; Saudek *et al.*, **1989**, *N. Engl. J Med.* 321:574).

In another embodiment, polymeric materials can be used (See "Medical  
15 Applications of Controlled Release," Langer and Wise (eds.), CRC Press., Boca Raton, Florida (1974); "Controlled Drug Bioavailability," Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Langer *et al.*, **1983**, *J Macromol. Sci. Rev. Macromol Chem.* 23:61; Levy *et al.*, **1985**, *Science* 228: 190; During *et al.*, **1989**, *Ann. Neurol.* 25:351; Howard *et al.*, **1989**, *J. Neurosurg.* 71:105). In a preferred embodiment,  
20 polymeric materials are used for oral sustained release delivery. Preferred polymers include sodium carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose (most preferred, hydroxypropylmethylcellulose). Other preferred cellulose ethers have been described (Alderman, *Int. J. Pharm. Tech. & Prod. Mfr.* **1984**, 5(3) 1-9). Factors affecting drug release are well known to the skilled artisan  
25 and have been described in the art (Bamba *et al.*, *Int. J. Pharm.* **1979**, 2, 307).

In another embodiment, enteric-coated preparations can be used for oral sustained release administration. Preferred coating materials include polymers with a pH-dependent solubility (*i.e.*, pH-controlled release), polymers with a slow or pH-dependent rate of swelling, dissolution or erosion (*i.e.*, time-controlled release), polymers that are degraded by  
30 enzymes (*i.e.*, enzyme-controlled release) and polymers that form firm layers that are destroyed by an increase in pressure (*i.e.*, pressure-controlled release).

In yet another embodiment, drug-releasing lipid matrices can be used for oral sustained release administration. One particularly preferred example is when solid

microparticles of the prodrug are coated with a thin controlled release layer of a lipid (*e.g.*, glyceryl behenate and/or glyceryl palmitostearate) as disclosed in Farah *et al.*, United States Patent No. 6,375,987 and Joachim *et al.*, United States Patent No. 6,379,700. The lipid-coated particles can optionally be compressed to form a tablet. Another controlled release lipid-based matrix material which is suitable for sustained release oral administration comprises polyglycolized glycerides as disclosed in Roussin *et al.*, United States Patent No. 6,171,615.

In yet another embodiment, prodrug-releasing waxes can be used for oral sustained release administration. Examples of suitable sustained prodrug-releasing waxes are disclosed in Cain *et al.*, United States Patent No. 3,402,240 (carnauba wax, candelilla wax, esparto wax and ouricury wax); Shtohryn *et al.* United States Patent No. 4,820,523 (hydrogenated vegetable oil, bees wax, caranuba wax, paraffin, candelilla, ozokerite and mixtures thereof); and Walters, United States Patent No. 4,421,736 (mixture of paraffin and castor wax).

In still another embodiment, osmotic delivery systems are used for oral sustained release administration (Verma *et al.*, *Drug Dev. Ind. Pharm.*, 2000, 26:695-708). In a preferred embodiment, OROS<sup>®</sup> systems made by Alza Corporation, Mountain View, CA are used for oral sustained release delivery devices (Theeuwes *et al.*, United States Patent No. 3,845,770; Theeuwes *et al.*, United States Patent No. 3,916,899).

In yet another embodiment, a controlled-release system can be placed in proximity of the target of the prodrug of the fused GABA analog, thus requiring only a fraction of the systemic dose (See, *e.g.*, Goodson, in "Medical Applications of Controlled Release," *supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in Langer, 1990, *Science* 249:1527-1533 may also be used.

In another embodiment of the invention, the dosage form comprises a prodrug of a fused GABA analog coated on a polymer substrate. The polymer can be an erodible, or a nonerodible polymer. The coated substrate may be folded onto itself to provide a bilayer polymer drug dosage form. For example, a prodrug of a fused GABA analog can be coated onto a polymer such as a polypeptide, collagen, gelatin, polyvinyl alcohol, polyorthoester, polyacetyl, or a polyorthocarbonate and the coated polymer folded onto itself to provide a bilaminated dosage form. In operation, the bioerodible dosage form erodes at a controlled rate to dispense the prodrug over a sustained release period. Representative biodegradable polymers comprise a member selected from the group consisting of biodegradable

poly(amides), poly (amino acids), poly(esters), poly(lactic acid), poly(glycolic acid), poly(carbohydrate), poly(orthoester), poly (orthocarbonate), poly(acetyl), poly(anhydrides), biodegradable poly(dihydropyrans), and poly(dioxinones) which are known in the art (Rosoff, *Controlled Release of Drugs*, Chap. 2, pp. 53-95 (1989); Heller *et al.*, United States Patent No. 3,811,444; Michaels, United States Patent No. 3,962,414; Capozza, United States Patent No. 4,066,747; Schmitt, United States Patent No. 4,070,347; Choi *et al.*, United States Patent No. 4,079,038; Choi *et al.*, United States Patent No. 4,093,709).

In another embodiment of the invention, the dosage form comprises a prodrug loaded into a polymer that releases the prodrug by diffusion through a polymer, or by flux through pores or by rupture of a polymer matrix. The drug delivery polymeric dosage form comprises a concentration of 10 mg to 2500 mg homogenously contained in or on a polymer. The dosage form comprises at least one exposed surface at the beginning of dose delivery. The non-exposed surface, when present, is coated with a pharmaceutically acceptable material impermeable to the passage of a prodrug. The dosage form may be manufactured by procedures known in the art. An example of providing a dosage form comprises blending a pharmaceutically acceptable carrier like polyethylene glycol, with a known dose of prodrug at an elevated temperature, (*e.g.*, 37 °C), and adding it to a silastic medical grade elastomer with a cross-linking agent, for example, octanoate, followed by casting in a mold. The step is repeated for each optional successive layer. The system is allowed to set for about 1 hour, to provide the dosage form. Representative polymers for manufacturing the dosage form comprise a member selected from the group consisting of olefin, and vinyl polymers, addition polymers, condensation polymers, carbohydrate polymers, and silicone polymers as represented by polyethylene, polypropylene, polyvinyl acetate, polymethylacrylate, polyisobutylmethacrylate, poly alginate, polyamide and polysilicone. The polymers and procedures for manufacturing them have been described in the art (Coleman *et al.*, *Polymers* 1990, 31, 1187-1231; Roerdink *et al.*, *Drug Carrier Systems* 1989, 9, 57-10.; Leong *et al.*, *Adv. Drug Delivery Rev.* 1987, 1, 199-233; Roff *et al.*, *Handbook of Common Polymers* 1971, CRC Press; Chien *et al.*, United States Patent No. 3,992,518).

In another embodiment of the invention, the dosage form comprises a plurality of tiny pills. The tiny time-release pills provide a number of individual doses for providing various time doses for achieving a sustained-release prodrug delivery profile over an

extended period of time up to 24 hours. The matrix comprises a hydrophilic polymer selected from the group consisting of a polysaccharide, agar, agarose, natural gum, alkali alginate including sodium alginate, carrageenan, fucoidan, furcellaran, laminaran, hypnea, gum arabic, gum ghatti, gum karaya, grum tragacanth, locust bean gum, pectin, amylopectin, gelatin, and a hydrophilic colloid. The hydrophilic matrix comprises a plurality of 4 to 50 tiny pills, each tiny pill comprise a dose population of from 10 ng, 0.5mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 5.0 mg *etc.* The tiny pills comprise a release rate-controlling wall of 0.001 mm up to 10 mm thickness to provide for the timed release of prodrug. Representative wall forming materials include a triglyceryl ester selected from the group consisting of glyceryl tristearate, glyceryl monostearate, glyceryl dipalmitate, glyceryl laureate, glyceryl didecenoate and glyceryl tridenoate. Other wall forming materials comprise polyvinyl acetate, phthalate, methylcellulose phthalate and microporous olefins. Procedures for manufacturing tiny pills are disclosed in Urquhart *et al.*, United States Patent No. 4,434,153; Urquhart *et al.*, United States Patent No. 4,721,613; Theeuwes, United States Patent No. 4,853,229; Barry, United States Patent No. 2,996,431; Neville, United States Patent No. 3,139,383; Mehta, United States Patent No. 4,752,470.

In another embodiment of the invention, the dosage form comprises an osmotic dosage form, which comprises a semipermeable wall that surrounds a therapeutic composition comprising the prodrug. In use within a patient, the osmotic dosage form comprising a homogenous composition, imbibes fluid through the semipermeable wall into the dosage form in response to the concentration gradient across the semipermeable wall. The therapeutic composition in the dosage form develops osmotic pressure differential that causes the therapeutic composition to be administered through an exit from the dosage form over a prolonged period of time up to 24 hours (or even in some cases up to 30 hours) to provide controlled and sustained prodrug release. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations.

In another embodiment of the invention, the dosage form comprises another osmotic dosage form comprising a wall surrounding a compartment, the wall comprising a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of prodrug present in the compartment, a prodrug-containing layer composition in the compartment, a hydrogel push layer composition in the compartment comprising an osmotic formulation for imbibing and absorbing fluid for

expanding in size for pushing the prodrug composition layer from the dosage form, and at least one passageway in the wall for releasing the prodrug composition. The method delivers the prodrug by imbibing fluid through the semipermeable wall at a fluid imbibing rate determined by the permeability of the semipermeable wall and the osmotic pressure across the semipermeable wall causing the push layer to expand, thereby delivering the prodrug from the dosage form through the exit passageway to a patient over a prolonged period of time (up to 24 or even 30 hours). The hydrogel layer composition may comprise 10 mg to 1000 mg of a hydrogel such as a member selected from the group consisting of a polyalkylene oxide of 1,000,000 to 8,000,000 which are selected from the group consisting of a polyethylene oxide of 1,000,000 weight-average molecular weight, a polyethylene oxide of 2,000,000 molecular weight, a polyethylene oxide of 4,000,000 molecular weight, a polyethylene oxide of 5,000,000 molecular weight, a polyethylene oxide of 7,000,000 molecular weight and a polypropylene oxide of the 1,000,000 to 8,000,000 weight-average molecular weight; or 10 mg to 1000 mg of an alkali carboxymethylcellulose of 10,000 to 6,000,000 weight average molecular weight, such as sodium carboxymethylcellulose or potassium carboxymethylcellulose. The hydrogel expansion layer comprises 0.0 mg to 350 mg, in present manufacture; 0.1 mg to 250 mg of a hydroxyalkylcellulose of 7,500 to 4,500,00 weight-average molecular weight (*e.g.*, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose or hydroxypentylcellulose) in present manufacture; 1 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol; 0 to 5 mg of a colorant, such as ferric oxide; 0 mg to 30 mg, in a present manufacture, 0.1 mg to 30 mg of a hydroxypropylalkylcellulose of 9,000 to 225,000 average-number molecular weight, selected from the group consisting of hydroxypropylethylcellulose, hydroxypropypentylcellulose, hydroxypropylmethylcellulose, and hydropropylbutylcellulose; 0.00 to 1.5 mg of an antioxidant selected from the group consisting of ascorbic acid, butylated hydroxyanisole, butylated hydroxyquinone, butylhydroxyanisol, hydroxycomarin, butylated hydroxytoluene, cephalin, ethyl gallate, propyl gallate, octyl gallate, lauryl gallate, propylhydroxybenzoate, trihydroxybutylrophenone, dimethylphenol, dibutylphenol, vitamin E, lecithin and ethanolamine; and 0.0 mg to 7 mg of a lubricant selected from the group consisting of calcium stearate, magnesium stearate, zinc stearate, magnesium oleate,

calcium palmitate, sodium suberate, potassium laurate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, a mixture of a salt of a fatty, alicyclic or aromatic acid, and a fatty, alicyclic, or aromatic acid.

5 In the osmotic dosage forms, the semipermeable wall comprises a composition that is permeable to the passage of fluid and impermeable to the passage of prodrug. The wall is nontoxic and comprises a polymer selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate. The wall comprises 75 wt % (weight percent) to 100 wt % of the cellulosic wall-forming polymer; or, the wall can comprise additionally 0.01 wt % to 80 wt % of  
10 polyethylene glycol, or 1 wt % to 25 wt % of a cellulose ether selected from the group consisting of hydroxypropylcellulose or a hydroxypropylalkylcellulose such as hydroxypropylmethylcellulose. The total weight percent of all components comprising the wall is equal to 100 wt %. The internal compartment comprises the prodrug-containing composition alone or in layered position with an expandable hydrogel composition. The  
15 expandable hydrogel composition in the compartment increases in dimension by imbibing the fluid through the semipermeable wall, causing the hydrogel to expand and occupy space in the compartment, whereby the drug composition is pushed from the dosage form. The therapeutic layer and the expandable layer act together during the operation of the dosage form for the release of prodrug to a patient over time. The dosage form comprises a  
20 passageway in the wall that connects the exterior of the dosage form with the internal compartment. The osmotic powered dosage form can be made to deliver prodrug from the dosage form to the patient at a zero order rate of release over a period of up to about 24 hours.

The expression "passageway" as used herein comprises means and methods  
25 suitable for the metered release of the prodrug from the compartment of the dosage form. The exit means comprises at least one passageway, including orifice, bore, aperture, pore, porous element, hollow fiber, capillary tube, channel, porous overlay, or porous element that provides for the osmotic controlled release of prodrug. The passageway includes a material that erodes or is leached from the wall in a fluid environment of use to  
30 produce at least one controlled-release dimensioned passageway. Representative materials suitable for forming a passageway, or a multiplicity of passageways comprise a leachable poly(glycolic) acid or poly(lactic) acid polymer in the wall, a gelatinous filament, poly(vinyl alcohol), leach-able polysaccharides, salts, and oxides. A pore passageway, or

more than one pore passageway, can be formed by leaching a leachable compound, such as sorbitol, from the wall. The passageway possesses controlled-release dimensions, such as round, triangular, square and elliptical, for the metered release of prodrug from the dosage form. The dosage form can be constructed with one or more passageways in spaced apart relationship on a single surface or on more than one surface of the wall. The expression "fluid environment" denotes an aqueous or biological fluid as in a human patient, including the gastrointestinal tract. Passageways and equipment for forming passageways are disclosed in Theeuwes *et al.*, United States Patent No. 3,845,770; Theeuwes *et al.*, United States Patent No. 3,916,899; Saunders *et al.*, United States Patent No. 4,063,064; Theeuwes *et al.*, United States Patent No. 4,088,864 and Ayer *et al.*, United States Patent No. 4,816,263. Passageways formed by leaching are disclosed in Ayer *et al.*, United States Patent No. 4,200,098 and Ayer *et al.*, United States Patent No. 4,285,987.

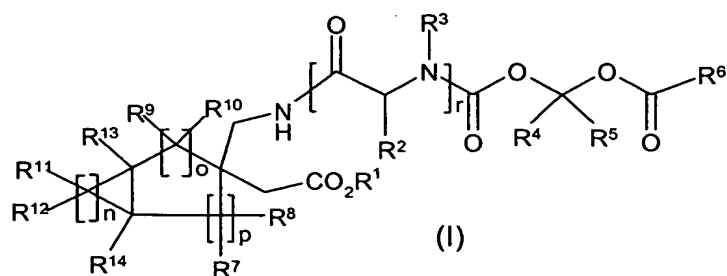
Regardless of the specific form of sustained release oral dosage form used, the prodrug is preferably released from the dosage form over a period of at least about 6 hours, more preferably, over a period of at least about 8 hours, and most preferably, over a period of at least about 12 hours. Further, the dosage form preferably releases from 0 to 20% of the prodrug in 0 to 2 hours, from 20 to 50% of the prodrug in 2 to 12 hours, from 50 to 85% of the prodrug in 3 to 20 hours and greater than 75% of the prodrug in 5 to 18 hours. The sustained release oral dosage form further provides a concentration of the fused GABA analog in the blood plasma of the patient over time, which curve has an area under the curve (AUC) that is proportional to the dose of the prodrug of fused GABA analog administered, and a maximum concentration  $C_{max}$ . The  $C_{max}$  is less than 75%, and is preferably, less than 60%, of the  $C_{max}$  obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form, and the AUC is substantially the same as the AUC obtained from administering an equivalent dose of the prodrug from an immediate release oral dosage form.

Preferably, the dosage forms of the invention are administered twice per day (more preferably, once per day).

#### **Prodrugs Useful in the Invention**

It should be understood that the present invention is not restricted to particular prodrugs of fused GABA analogs. Accordingly, the present invention may be practiced with any fused GABA analog prodrug.

A preferred class of fused GABA analog prodrugs particularly useful in the present invention includes the following compounds. In a first embodiment, the compounds of structural Formula (I) are useful in the present invention:



5 or a pharmaceutically acceptable salt, hydrate, solvate or N-oxide thereof, wherein:

n is 1, 2, 3, 4, 5 or 6;

o is 0, 1, 2 or 3;

10

p is 0, 1 or 2;

r is 0 or 1;

15

R<sup>1</sup> and R<sup>3</sup> are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl;

20

R<sup>2</sup> is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, acylamino, substituted acylamino, alkylamino, substituted alkylamino, aryl, substituted aryl, arylalkyl, substituted arylalkyl, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, dialkylamino, substituted dialkylamino, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, oxycarbonyl or substituted oxycarbonyl, or optionally, R<sup>2</sup> and R<sup>3</sup> together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring;

25

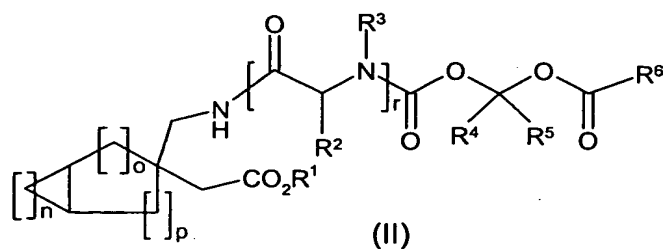


$R^4$  and  $R^5$  are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, cycloalkoxycarbonyl, substituted cycloalkoxycarbonyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, oxycarbonyl or substituted oxycarbonyl or optionally,  $R^4$  and  $R^5$  together with the carbon atom to which they are bonded form a cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl ring;

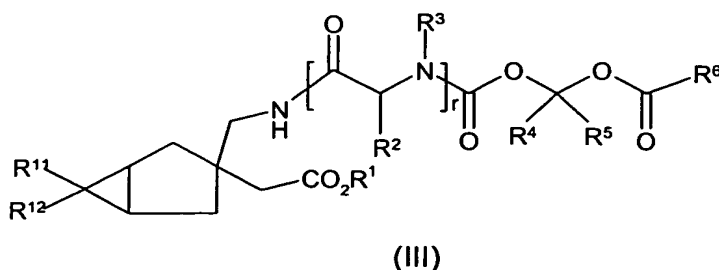
$R^6$  is acyl, substituted acyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl; and

each of  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  is independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl or substituted heteroarylalkyl.

In a second embodiment, the compounds of structural Formula (II) are useful in the present invention:



In a third embodiment, the compounds of structural Formula (III) are useful in the present invention:



wherein each of  $R^{11}$  and  $R^{12}$  is independently hydrogen or methyl.

In a fourth embodiment, the compounds of structural formula (III) are derived from a fused GABA analog selected from the group consisting of

(3-Aminomethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid,

5 (1 $\alpha$ , 3 $\alpha$ , 5 $\alpha$ )-(3-Aminomethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid,

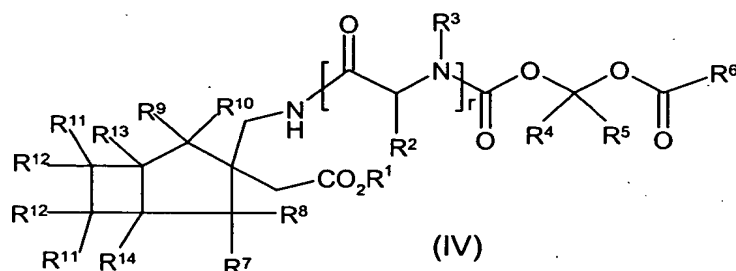
(1 $\alpha$ , 5 $\beta$ )-(3-Aminomethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid,

(1 $\alpha$ , 3 $\beta$ , 5 $\alpha$ )-(3-Aminomethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid,

((1R, 5S)-3-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid and

((1S, 5R)-3-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-3-yl)-acetic acid.

10 In a fifth embodiment, the present invention the compounds of structural Formula (IV) are useful in the present invention:



wherein each of  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  is independently hydrogen or methyl.

In a sixth embodiment, compounds of structural Formula (IV) are derived from a fused GABA analog selected from the group consisting of

15 (3-Aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

(1 $\alpha$ , 3 $\alpha$ , 5 $\alpha$ )-(3-Aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

(1 $\alpha$ , 5 $\beta$ )-(3-Aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

(1 $\alpha$ , 3 $\beta$ , 5 $\alpha$ )-(3-Aminomethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

20 ((1R, 5S)-3-Aminomethyl-1,5-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

((1S, 5R)-3-Aminomethyl-1,5-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

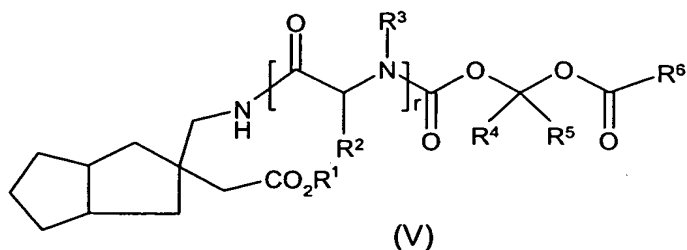
*cis*-((1S, 2R, 4S, 5R)-3-Aminomethyl-2,4-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

*trans*-((1S, 2R, 4S, 5R)-3-Aminomethyl-2,4-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid,

((1S, 5R, 6S, 7R)-3-Aminomethyl-6,7-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid and

25 ((1S, 5R, 6R, 7S)-3-Aminomethyl-6,7-dimethyl-bicyclo[3.2.0]hept-3-yl)-acetic acid.

In a seventh embodiment, compounds having structural Formula (V) are useful in the present invention:



In a eighth embodiment, compounds of structural Formula (V) are derived from a fused GABA analog selected from the group consisting of

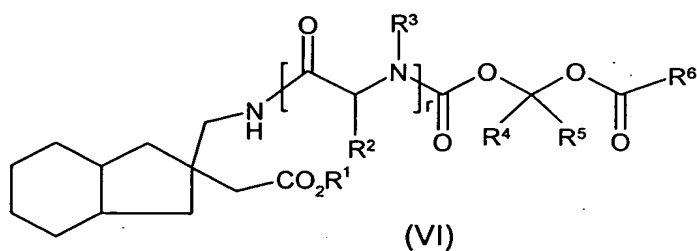
(2-Aminomethyl-octahydro-pentalen-2-yl)-acetic acid,

5 (1 $\alpha$ , 3 $\alpha$ , 5 $\alpha$ )-(2-Aminomethyl-octahydro-pentalen-2-yl)-acetic acid,

(1 $\alpha$ , 5 $\beta$ )-(2-Aminomethyl-octahydro-pentalen-2-yl)-acetic acid and

(1 $\alpha$ , 3 $\beta$ , 5 $\alpha$ )-(2-Aminomethyl-octahydro-pentalen-2-yl)-acetic acid.

In a ninth embodiment, compounds having structural Formula (VI) are useful in the present invention:



In a tenth embodiment, compounds of structural Formula (VI) are derived from a fused GABA analog selected from the group consisting of

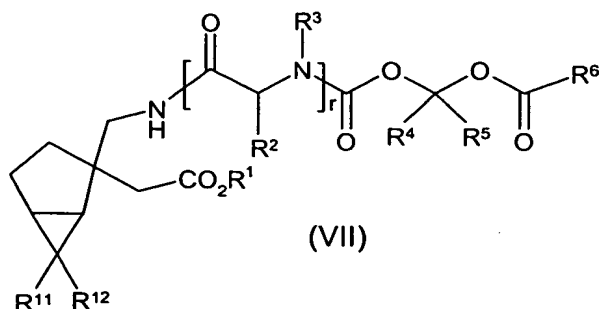
(2-Aminomethyl-octahydro-inden-2-yl)-acetic acid,

(1 $\alpha$ , 6 $\alpha$ , 8 $\alpha$ )-(2-Aminomethyl-octahydro-inden-2-yl)-acetic acid,

15 (1 $\alpha$ , 6 $\beta$ )-(2-Aminomethyl-octahydro-inden-2-yl)-acetic acid and

(1 $\alpha$ , 6 $\alpha$ , 8 $\beta$ )-(2-Aminomethyl-octahydro-inden-2-yl)-acetic acid.

In a eleventh embodiment, compounds having structural Formula (VII) are useful in the present invention:

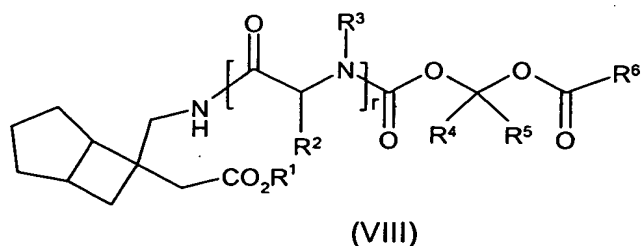


wherein R<sup>11</sup> and R<sup>12</sup> are independently hydrogen or methyl.

In a twelfth embodiment, compounds of structural Formula (VII) are derived from a fused GABA analog selected from the group consisting of

- 5 (2-Aminomethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid,  
((1S, 2S, 5R)-2-Aminomethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid,  
((1R, 2S, 5S)-2-Aminomethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid,  
((1S, 2R, 5R)-2-Aminomethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid,  
((1R, 2R, 5S)-2-Aminomethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid,  
10 (2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid,  
((1S, 2S, 5R)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid,  
((1R, 2S, 5S)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid,  
((1S, 2R, 5R)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid and  
((1R, 2R, 5S)-2-Aminomethyl-6,6-dimethyl-bicyclo[3.1.0]hex-2-yl)-acetic acid.

15 In a thirteenth embodiment, compounds having structural Formula (VIII) are useful in the present invention:

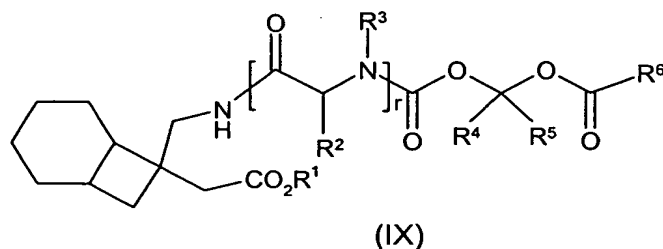


In a fourteenth embodiment, compounds of structural Formula (VIII) are derived from a fused GABA analog selected from the group consisting of

- 20 (6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid,  
((1R, 5R, 6S)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid,  
((1S, 5S, 6S)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid,  
((1R, 5R, 6R)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid and

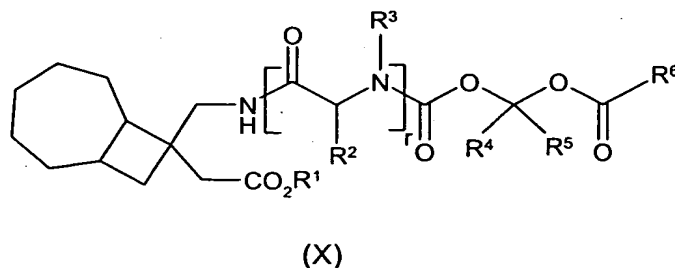
((1S, 5S, 6R)-6-Aminomethyl-bicyclo[3.2.0]hept-6-yl)-acetic acid.

In a fifteenth embodiment, compounds having structural Formula (IX) are useful in the present invention:



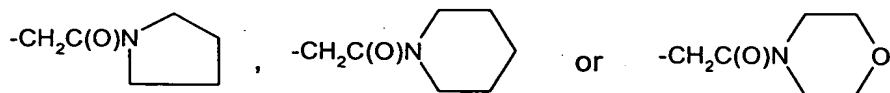
- 5 In a sixteenth embodiment, compounds of structural Formula (IX) are derived from a fused GABA analog selected from the group consisting of
- (7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid,
- ((1R, 6R, 7S)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid,
- ((1S, 6S, 7S)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid,
- 10 ((1R, 6R, 7R)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid and
- ((1S, 6S, 7R)-7-Aminomethyl-bicyclo[4.2.0]oct-7-yl)-acetic acid.

In a seventeenth embodiment, the present invention provides compounds of structural Formula (X):



- 15 In an eighteenth embodiment, the present invention provides compounds of structural Formula (X) derived from fused GABA analogs selected from the group consisting of
- (1R, 7R, 8S)-8-aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid,
- ((1S, 7S, 8S)-8-aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid,
- ((1R, 7R, 8R)-8-aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid and
- 20 ((1S, 7S, 8R)-8-aminomethyl-bicyclo[5.2.0]non-8-yl)-acetic acid.

Preferably, in the above embodiments, R<sup>1</sup> is hydrogen. Alternatively, R<sup>1</sup> may be hydrogen, alkanyl, substituted alkanyl, alkenyl, substituted alkenyl, aryl, substituted aryl, arylalkyl or substituted arylalkyl. Preferably, R<sup>1</sup> is hydrogen, methyl, ethyl, benzyl, -C(CH<sub>3</sub>)=CH<sub>2</sub>, -CH<sub>2</sub>C(O)N(CH<sub>3</sub>)<sub>2</sub>,



Metabolism of fused GABA analog prodrugs encompassed in the first eighteen embodiments above typically liberates the fused GABA analog along with one equivalent of an aldehyde or ketone (*i.e.*,  $\text{R}^4\text{R}^5\text{C}(\text{O})$ ). The instant invention provides a preferred method of orally administering fused GABA analog prodrugs where the byproduct aldehyde or ketone (*e.g.*, formaldehyde where  $\text{R}^4$  and  $\text{R}^5$  are hydrogen) exhibits significant mammalian toxicity.

Preferably, in the first eighteen embodiments above,  $\text{R}^2$  is hydrogen, alkanyl, substituted alkanyl, aryl, substituted aryl, arylalkanyl, substituted arylalkanyl, cycloalkanyl, heteroarylalkyl or substituted heteroarylalkanyl. More preferably,  $\text{R}^2$  is hydrogen, alkanyl or cycloalkanyl. Even more preferably,  $\text{R}^2$  is selected from the group consisting of hydrogen, methyl, isopropyl, isobutyl, *sec*-butyl, *t*-butyl, cyclopentyl and cyclohexyl.

Preferably, in the first eighteen embodiments above,  $\text{R}^2$  is selected from the group consisting of substituted alkanyl. More preferably,  $\text{R}^2$  is selected from the group consisting of  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}(\text{OH})\text{CH}_3$ ,  $-\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CONH}_2$ ,  $-\text{CH}_2\text{CH}_2\text{CONH}_2$ ,  $-\text{CH}_2\text{CH}_2\text{SCH}_3$ ,  $-\text{CH}_2\text{SH}$ ,  $-\text{CH}_2(\text{CH}_2)_3\text{NH}_2$  and  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(\text{NH})\text{NH}_2$ .

Preferably, in the first eighteen embodiments above,  $\text{R}^2$  is selected from the group consisting of aryl, arylalkanyl, substituted arylalkanyl and heteroarylalkanyl. More preferably,  $\text{R}^2$  is selected from the group consisting of phenyl, benzyl, 4-hydroxybenzyl, 4-bromobenzyl, 4-imidazolylmethyl and 3-indolylmethyl.

Preferably, in the first eighteen embodiments above,  $\text{R}^2$  and  $\text{R}^3$  together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring. More preferably,  $\text{R}^2$  and  $\text{R}^3$  together with the atoms to which they are bonded form an azetidine, pyrrolidine or piperidine ring.

Preferably, in the first eighteen embodiments above,  $\text{R}^3$  is hydrogen, alkyl, substituted alkyl, arylalkyl or substituted arylalkyl. More preferably,  $\text{R}^3$  is hydrogen, methyl, ethyl or benzyl.

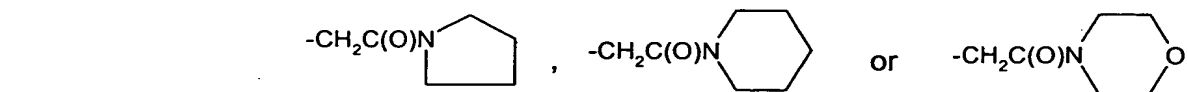
Preferably, in the first eighteen embodiments above,  $\text{R}^4$  and  $\text{R}^5$  are independently hydrogen, alkyl, substituted alkyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl or substituted heteroaryl. More preferably,  $\text{R}^4$  and  $\text{R}^5$  are independently hydrogen, alkyl, alkoxycarbonyl, aryl, arylalkyl or heteroaryl. More preferably,  $\text{R}^4$  and  $\text{R}^5$  are independently hydrogen, methyl, ethyl, propyl,

isopropyl, *sec*-butyl, *tert*-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, 3-pyridyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, *sec*-butoxycarbonyl, *tert*-butoxycarbonyl or cyclohexyloxycarbonyl.

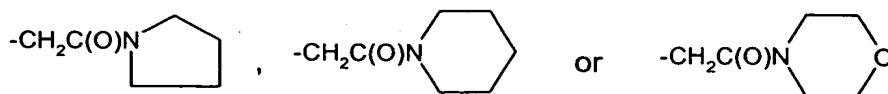
5 Preferably, in the first eighteen embodiments above, R<sup>6</sup> is acyl, substituted acyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heteroaryl or substituted heteroaryl. More preferably, R<sup>6</sup> is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 10 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 15 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or 3-pyridyl.

Preferably, in the first embodiment above, each of R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> is independently hydrogen, alkyl or substituted alkyl. More preferably, each of R<sup>7</sup>, R<sup>8</sup>,  
 20 R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> is independently hydrogen or methyl.

Preferably, in the first eighteen embodiments above, R<sup>1</sup> is hydrogen and R<sup>2</sup> and R<sup>3</sup> together with the atoms to which they are attached form a pyrrolidine ring. Preferably, in this embodiment, R<sup>1</sup> is hydrogen. Alternatively, R<sup>1</sup> is methyl, ethyl, benzyl, -C(CH<sub>3</sub>)=CH<sub>2</sub>, -CH<sub>2</sub>C(O)N(CH<sub>3</sub>)<sub>2</sub>,



Preferably, in the first eighteen embodiments above, R<sup>3</sup> is hydrogen and R<sup>2</sup> is selected from the group consisting of hydrogen, methyl, 2-propyl, 2-butyl, isobutyl, *tert*-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, 4-hydroxybenzyl, 4-bromobenzyl, 4-imidazolylmethyl, 3-indolylmethyl, -CH<sub>2</sub>OH, -CH(OH)CH<sub>3</sub>, -CH<sub>2</sub>CO<sub>2</sub>H, -CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H,  
 30 -CH<sub>2</sub>CONH<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>CONH<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>SCH<sub>3</sub>, -CH<sub>2</sub>SH, -CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub> and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NHC(NH)NH<sub>2</sub>. Preferably, in this embodiment, R<sup>1</sup> is hydrogen. Alternatively, R<sup>1</sup> is methyl, ethyl, benzyl, -C(CH<sub>3</sub>)=CH<sub>2</sub>, -CH<sub>2</sub>C(O)N(CH<sub>3</sub>)<sub>2</sub>,



Preferably, in the first eighteen embodiments above,  $R^1$  is hydrogen, alkanyl, substituted alkanyl, alkenyl, substituted alkenyl, aryl, substituted aryl, arylalkyl or substituted arylalkyl,  $R^2$  is hydrogen, alkanyl, substituted alkanyl, aryl, substituted aryl, arylalkanyl, substituted arylalkanyl, cycloalkanyl, heteroarylalkyl or substituted heteroarylalkanyl or optionally  $R^2$  and  $R^3$  together with the atoms to which they are bonded form a cycloheteroalkyl or substituted cycloheteroalkyl ring,  $R^3$  is hydrogen, alkyl, substituted alkyl, arylalkyl or substituted arylalkyl,  $R^4$  and  $R^5$  are independently hydrogen, alkyl, substituted alkyl, alkoxycarbonyl, substituted alkoxycarbonyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl or substituted heteroaryl and  $R^6$  is acyl, substituted acyl, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heteroaryl or substituted heteroaryl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is methyl,  $R^1$  and  $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl, 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is ethyl,  $R^1$  and  $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 1-(1,3-dioxan-2-yl)-benzyl,



1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl, 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

5 Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is propyl,  $R^1$  and  $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 10 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl, 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, 15 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is isopropyl,  $R^1$  and  $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 20 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 25 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl, 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is butyl,  $R^1$  and  $R^5$  are 30 hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl,

1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl,  
 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl,  
 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 1-(1,3-dioxan-2-yl)-benzyl,  
 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl, 1-(1,3-dioxolan-2-yl)-2-phenethyl,  
 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, butyryl, benzoyl, phenacetyl, phenyl,  
 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl,  
 cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is isobutyl,  $R^1$  and  $R^5$   
 are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,  
 isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is *sec*-butyl,  $R^1$  and  $R^5$   
 are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,  
 isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is *tert*-butyl,  $R^1$  and  
 $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,

isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 5 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
 10 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl. It should be noted that in  
 this embodiment, metabolism of this group of prodrugs may liberate the fused GABA  
 analog along with an equivalent of pivaldehyde, which may be oxidized to pivalic acid *in*  
*situ*.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is cyclopentyl,  $R^1$  and  
 15  $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,  
 isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 20 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
 25 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is cyclohexyl,  $R^1$  and  
 $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,  
 isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 30 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,

1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

- 5            Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is phenyl,  $R^1$  and  $R^5$   
are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,  
isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
10 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
15 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

- Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is benzyl,  $R^1$  and  $R^5$   
are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,  
isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
20 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
25 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

- Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is phenethyl,  $R^1$  and  
30  $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,  
isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,

1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
5 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is 3-pyridyl,  $R^1$  and  
 $R^5$  are hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl,  
10 isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
15 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

20 Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is methyl,  $R^5$  is  
methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl,  
propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
25 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
30 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is methoxycarbonyl,  
 $R^5$  is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl,

propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 5 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
 10 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is ethoxycarbonyl,  $R^5$   
 is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl,  
 propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 15 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 20 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^3$  is propoxycarbonyl,  
 $R^4$  is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl,  
 25 propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 30 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,

butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is isopropoxycarbonyl,  $R^5$  is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl, 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is butoxycarbonyl,  $R^5$  is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl, 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is isobutoxycarbonyl,  $R^5$  is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,

1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
5 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is *sec*-butoxycarbonyl,  
 $R^5$  is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group consisting of methyl, ethyl,  
propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl,  
1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
10 1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
15 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is  
*tert*-butoxycarbonyl,  $R^5$  is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group  
20 consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl,  
*sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,  
1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
25 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

30 Preferably, in the first eighteen embodiments above,  $r$  is 0,  $R^4$  is  
cyclohexyloxycarbonyl,  $R^5$  is methyl,  $R^1$  is hydrogen and  $R^6$  is selected from the group  
consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, pentyl, isopentyl,  
*sec*-pentyl, neopentyl, 1,1-dimethoxyethyl, 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl,



1-(1,3-dioxan-2-yl)-ethyl, 1,1-dimethoxypropyl, 1,1-diethoxypropyl,  
 1-(1,3-dioxolan-2-yl)-propyl, 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl,  
 1,1-diethoxybutyl, 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl,  
 1,1-dimethoxybenzyl, 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl,  
 5 1-(1,3-dioxan-2-yl)-benzyl, 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl,  
 1-(1,3-dioxolan-2-yl)-2-phenethyl, 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl,  
 butyryl, benzoyl, phenacetyl, phenyl, 4-methoxyphenyl, benzyl, phenethyl, styryl,  
 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and 3-pyridyl.

Preferably, in the first eighteen embodiments above,  $r$  is 0, each of  $R^1$ ,  $R^4$  and  $R^5$  is  
 10 hydrogen, and  $R^6$  is selected from the group consisting of methyl, ethyl, propyl, isopropyl,  
 butyl, isobutyl, *sec*-butyl, pentyl, isopentyl, *sec*-pentyl, neopentyl, 1,1-dimethoxyethyl,  
 1,1-diethoxyethyl, 1-(1,3-dioxolan-2-yl)-ethyl, 1-(1,3-dioxan-2-yl)-ethyl,  
 1,1-dimethoxypropyl, 1,1-diethoxypropyl, 1-(1,3-dioxolan-2-yl)-propyl,  
 1-(1,3-dioxan-2-yl)-propyl, 1,1-dimethoxybutyl, 1,1-diethoxybutyl,  
 15 1-(1,3-dioxolan-2-yl)-butyl, 1-(1,3-dioxan-2-yl)-butyl, 1,1-dimethoxybenzyl,  
 1,1-diethoxybenzyl, 1-(1,3-dioxolan-2-yl)-benzyl, 1-(1,3-dioxan-2-yl)-benzyl,  
 1,1-dimethoxy-2-phenethyl, 1,1-diethoxy-2-phenethyl, 1-(1,3-dioxolan-2-yl)-2-phenethyl,  
 1-(1,3-dioxan-2-yl)-2-phenethyl, acetyl, propionyl, butyryl, benzoyl, phenacetyl, phenyl,  
 4-methoxyphenyl, benzyl, phenethyl, styryl, cyclopropyl, cyclobutyl, cyclopentyl,  
 20 cyclohexyl and 3-pyridyl. It should be noted that in this embodiment, metabolism of this  
 group of prodrugs may liberate the fused GABA analog along with an equivalent of  
 formaldehyde.

Preferably, in the first eighteen embodiments above,  $R^3$  is hydrogen, and  $R^2$  is  
 selected from the group consisting of hydrogen, methyl, 2-propyl, 2-butyl, isobutyl,  
 25 *tert*-butyl, cyclopentyl, cyclohexyl, phenyl, benzyl, 4-hydroxybenzyl, 4-bromobenzyl,  
 4-imidazolylmethyl, 3-indolylmethyl,  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}(\text{OH})\text{CH}_3$ ,  $-\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ,  
 $-\text{CH}_2\text{CONH}_2$ ,  $-\text{CH}_2\text{CH}_2\text{CONH}_2$ ,  $-\text{CH}_2\text{CH}_2\text{SCH}_3$ ,  $-\text{CH}_2\text{SH}$ ,  $-\text{CH}_2(\text{CH}_2)_3\text{NH}_2$  and  
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(\text{NH})\text{NH}_2$ .

### 30 Synthesis of The Prodrugs used in the Invention

Those of skill in the art will appreciate that a preferred synthetic route to the  
 compounds of the invention will consist of attaching promoieties to fused GABA analogs.  
 Methods have been described in the art for the synthesis of fused GABA analogs

(Blakemore *et al.*, International Publication No. WO 02/085839; Blakemore *et al.*, International Publication No. WO 02/090318). Other methods will be apparent to the skilled artisan for synthesizing fused GABA analogs in view of the references provided above. The promoieties described herein, are known in the art and may be prepared and attached to fused GABA analogs by established procedures (See *e.g.*, Green *et al.*,  
5 "Protective Groups in Organic Chemistry", (Wiley, 2<sup>nd</sup> ed. 1991); Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; and Paquette, "Encyclopedia of Reagents for Organic Synthesis," John Wiley & Sons, 1995).  
10 Preferably, the promoieties illustrated herein, may be attached to fused GABA analogs by the procedures described in Cundy *et al.*, United States Patent Application Serial No. 10/710,127, filed June 11, 2002; Gallop *et al.*, United States Patent Application Serial No. 10/171,485, filed June 11, 2002; and Gallop *et al.*, United States Patent Application Serial No. 10/167,197, filed June 11, 2002.

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#### **Therapeutic Uses of the Dosage Forms of the Invention**

In accordance with the invention, an extended release oral dosage form of the invention is administered to a patient, preferably a human, suffering from epilepsy, depression, anxiety, psychosis, faintness attacks, hypokinesia, cranial disorders,  
20 neurodegenerative disorders, panic, pain (especially, neuropathic pain and muscular and skeletal pain), inflammatory disease (*i.e.*, arthritis), insomnia, gastrointestinal disorders, hot flashes, restless legs syndrome, urinary incontinence or ethanol withdrawal syndrome. Further, in certain embodiments, the dosage forms of the invention are administered to a patient, preferably a human, as a preventative measure against various diseases or disorders.  
25 Thus, the dosage forms of the invention may be administered as a preventative measure to a patient having a predisposition for epilepsy, depression, anxiety, psychosis, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, panic, pain (especially, neuropathic pain and muscular and skeletal pain), inflammatory disease (*i.e.*, arthritis), insomnia, gastrointestinal disorders, hot flashes, restless legs syndrome, urinary  
30 incontinence or ethanol withdrawal syndrome. Accordingly, the dosage forms of the invention may be used for the prevention of one disease or disorder and concurrently treating another (*e.g.*, prevention of psychosis while treating gastrointestinal disorders; prevention of neuropathic pain while treating ethanol withdrawal syndrome).

The suitability of the dosage forms of the invention in treating epilepsy, depression, anxiety, psychosis, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, panic, pain (especially neuropathic pain and muscular and skeletal pain), inflammatory disease (*i.e.*, arthritis), insomnia, gastrointestinal disorders hot flashes, restless legs syndrome, urinary incontinence and ethanol withdrawal syndrome may be determined by methods described in the art (See, *e.g.*, Satzinger *et al.*, United States Patent No. 4,024,175; Satzinger *et al.*, United States Patent No. 4,087,544; Woodruff, United States Patent No. 5,084,169; Silverman *et al.*, United States Patent No. 5,563,175; Singh, United States Patent No. 6,001,876; Horwell *et al.*, United States Patent No. 6,020,370; Silverman *et al.*, United States Patent No. 6,028,214; Horwell *et al.*, United States Patent No. 6,103,932; Silverman *et al.*, United States Patent No. 6,117,906; Silverman, International Publication No. WO 92/09560; Silverman *et al.*, International Publication No. WO 93/23383; Horwell *et al.*, International Publication No. WO 97/29101, Horwell *et al.*, International Publication No. WO 97/33858; Horwell *et al.*, International Publication No. WO 97/33859; Bryans *et al.*, International Publication No. WO 98/17627; Guglietta *et al.*, International Publication No. WO 99/08671; Bryans *et al.*, International Publication No. WO 99/21824; Bryans *et al.*, International Publication No. WO 99/31057; Magnus-Miller *et al.*, International Publication No. WO 99/37296; Bryans *et al.*, International Publication No. WO 99/31075; Bryans *et al.*, International Publication No. WO 99/61424; Pande, International Publication No. WO 00/23067; Bryans, International Publication No. WO 00/31020; Bryans *et al.*, International Publication No. WO 00/50027; and Bryans *et al.*, International Publication No. WO 02/00209).

Accordingly, it is well with the capability of those of skill in the art to assay and use the compounds of the invention and/or pharmaceutical compositions thereof to treat or prevent the above diseases or disorders.

#### **Therapeutic/Prophylactic Administration**

The dosage forms of the invention may be advantageously used in human medicine. As previously described, the dosage forms of the invention are useful for the treatment or prevention of epilepsy, depression, anxiety, psychosis, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, panic, pain (especially, neuropathic pain and muscular and skeletal pain), inflammatory disease (*i.e.*, arthritis), insomnia, gastrointestinal

disorders, hot flashes, restless legs syndrome, urinary incontinence or ethanol withdrawal syndrome.

When used to treat or prevent the above disease or disorders the dosage forms of the invention may be administered or applied singly, or in combination with other agents. The dosage forms of the invention may also deliver a fused GABA analog prodrug in combination with another pharmaceutically active agent, including another fused GABA analog prodrug.

The current invention provides methods of treatment and prophylaxis by administration to a patient a fused GABA analog prodrug dosage form of the present invention. The patient may be an animal, is more preferably a mammal, and most preferably a human.

The dosage forms of the invention, upon releasing the fused GABA analog prodrug, preferably provide fused GABA analogs upon *in vivo* administration to a patient. While not wishing to bound by theory, the promoiety or promoieties of the prodrug may be cleaved either chemically and/or enzymatically. One or more enzymes present in the stomach, intestinal lumen, intestinal tissue, blood, liver, brain or any other suitable tissue of a mammal may enzymatically cleave the promoiety or promoieties of the prodrug. The mechanism of cleavage is not important to the current invention.

While not wishing to bound by theory, the promoiety or promoieties may be cleaved prior to absorption by the gastrointestinal tract (*e.g.*, within the stomach or intestinal lumen) and/or after absorption by the gastrointestinal tract (*e.g.*, in intestinal tissue, blood, liver or other suitable tissue of a mammal). If the promoiety or promoieties are cleaved prior to absorption by the gastrointestinal tract, the resulting fused GABA analogs may be absorbed into the systemic circulation conventionally (*e.g.*, *via* an amino acid transporter located in the small intestine). If the promoiety or promoieties are cleaved after absorption by the gastrointestinal tract, these fused GABA analog prodrugs may have the opportunity to be absorbed into the systemic circulation either by passive diffusion, active transport or by both passive and active processes.

If the promoiety or promoieties are cleaved after absorption by the gastrointestinal tract, these fused GABA analog prodrugs may have the opportunity to be absorbed into the systemic circulation from the large intestine. It is preferred that the promoiety or promoieties are cleaved after absorption by the gastrointestinal tract.

### **Pharmaceutical Compositions Useful in the Invention**

The present pharmaceutical compositions contain a therapeutically effective amount of one or more fused GABA analog prodrugs, preferably in purified form, together with a suitable amount of a pharmaceutically acceptable vehicle, so as to provide the form for proper administration to a patient. When administered to a patient, the prodrug and pharmaceutically acceptable vehicles are preferably sterile. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present pharmaceutical compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used.

### **Methods of Use And Doses**

The extended release oral dosage forms of fused GABA analog prodrugs are administered to treat or prevent diseases or disorders such as epilepsy, depression, anxiety, psychosis, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, panic, pain (especially neuropathic pain and muscular and skeletal pain), inflammatory disease (*i.e.*, arthritis), insomnia, gastrointestinal disorders, hot flashes, restless legs syndrome, urinary incontinence or ethanol withdrawal syndrome.

The amount of fused GABA analog prodrug that will be effective in the treatment of a particular disorder or condition disclosed herein will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques known in the art as previously described. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The amount of a prodrug administered will, of course, be dependent on, among other factors, the subject being treated, the weight of the subject, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

Preferably, the dosage forms of the invention are adapted to be administered to a patient no more than twice per day, more preferably, only once per day. Dosing may be provided alone or in combination with other drugs and may continue as long as required for effective treatment of the disease state or disorder.

Suitable dosage ranges for oral administration are dependent on the potency of the parent fused GABA analog, but are generally between about 0.001 mg to about 200 mg of a compound of the invention per kilogram body weight. Other fused GABA analogs may be more potent and lower doses may be appropriate for both the parent drug and any prodrug (measured on an equivalent molar basis). Dosage ranges may be readily determined by methods known to the skilled artisan.

The prodrugs used in the invention are preferably assayed *in vitro* and *in vivo*, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays can be used to determine whether administration of a specific prodrug or a combination of prodrugs is preferred for reducing convulsion. The prodrugs may also be demonstrated to be effective and safe using animal model systems.

Finally, it should be noted that there are alternative ways of implementing both the present invention. Accordingly, the present embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

All publications and patents cited herein are incorporated by reference in their entirety.